Impact of different organic acids on solubility enhancement of cefpodxime proxetil immediate release tablet and its stability studies

Sabahat Jabeen, Fouzia Hassan, Rabia Ismail Yousuf, Muhammad Harris Shoaib, Fozia Israr, Syed Muhammad Farid Hasan, Rehana Saeed and Sadaf Farooqi
Department of Pharmaceutics, Faculty of Pharmacy & Pharmaceutical Sciences, University of Karachi, Karachi, Pakistan

Abstract: Cefpodoxime proxetil is a third generation cephalosporin antibiotic demonstrates pH dependent solubility and is highly soluble only in acidic pH. The purpose of this investigation was to design and develop immediate release tablets of cefpodoxime proxetil by direct compression method and determine the effect of different solid buffers (organic acids) such as fumaric acid (formulations F1-F4), maleic acid (formulations M1-M4) and citric acid (formulations C1-C4) by using cefpodoxime and acid in the ratios of 4:1, 2:1, 1:1 and 1:2 to achieve pH-independent release of the drug. Physical parameters and assay were found to be within the acceptable range as prescribed in USP 36 / NF 31. In vitro dissolution studies of each formulation were performed in distilled water, USP dissolution medium, HCl buffer solution of pH 1.2, phosphate buffer solutions of pH 4.5 and 6.8 to observe the drug release. The formulations F3, F4, M4 were selected for film coating on the basis of better drug release profile, to protect the drug from chemical degradation through hydrolysis. Film coated formulation F3, F4 and M4 showed a remarkable in vitro release of the drug (72.88±0.43 to 92.67±0.71%) within 30min of observation in all dissolution media and further evaluated by model independent and model dependent approaches. The drug release was found to be best fit to Weibull model as highest r^2_{adjusted} (0.924-0.998) and lowest AIC (18.416-54.710) values were obtained in all dissolution media. R Gui® applied for stability studies of F3 and F4 formulations, showing shelf lives of 28 & 27months at ambient and 33 months at accelerated temperatures. Formulation F4 was chosen as best formulation on the basis of physical properties, highest dissolution rate and stability studies.

Keywords: Cefpodoxime proxetil, organic acids, film coating, *in vitro* dissolution, stability studies.

INTRODUCTION

The effectiveness of a drug mainly depends on its solubility and intestinal permeability. Solubility is one of the most important property to get the required concentration of the drug in systemic circulation for its pharmacological action (James, 1986). The number of drugs having low solubility has been increased and 70% of new drug candidates have been shown poor aqueous solubility (Ku and Dulin, 2012). Poorly water soluble drugs are associated with slow drug absorption leading eventually to inadequate and variable bioavailability (Ahuja *et al*., 2007)

The biopharmaceutical classification system categorizes the drug substances on the basis of their aqueous solubility and intestinal permeability in to four major groups (Class I -IV) (FDA, 2000). Cefpodoxime proxetil is an oral third generation cephalosporin antibiotic having BCS class IV qualities with a poor aqueous solubility of ~400µg/ml and absolute bioavailability of 50% only (Date and Nagarsenker, 2007, Sharma *et al*., 2011) The absorption of cefpodoxime proxetil occurs in gastrointestinal tract, where it is deesterified to its active form cefpodoxime and releases into the systemic circulations (Banerjee and Singh, 2013). Cefpodoxime acts by inhibition of bacterial cell wall synthesis causing acylation of membrane bound transpeptidase enzymes results in reduction of peptidoglycans. (Palparthi and Reddy, 2013).

Drug solubility, dissolution and intestinal permeability are three major factors that mainly contribute in oral absorption and bioavailability of cephalosporin compounds. There are various methods to improve the solubility of poorly soluble drugs such as solvent deposition, solid dispersion, eutectic mixture, micronization, use of surfactant and molecular encapsulation etc. (Israr *et al*., 2014). As mostly drugs are weak acids or bases and their solubility is pH dependent in GI tract. Therefore, drug release from a dosage forms depends on the Henderson-Hasselbalch equation (Preechagoon *et al*., 2000). Many attempts have been made to solve this problem of pH dependent solubility of the drugs by using organic acids. Incorporation of these acidifiers modifies the micro environmental pH around the drug particles throughout GIT, increasing the ionization of the drug and thus its dissolution rate (Bolourchian and Dadashzadeh, 2008).

The aim of present study was to,

- develop formulations of cefpodoxime proxetil tablets by incorporation of solid acid buffers such as fumaric acid, maleic acid, and citric acid to enhance its solubility and dissolution rate by direct compression

*Corresponding author: e-mail: sabahatjabeen_uok@hotmail.com

method,
- evaluate quality of these formulations through pharmacopoeial and non pharmacopoeial tests,
- compare these formulations with a reference brand available in local market by a model dependent and independent approaches and,
- perform stability studies and predict shelf life of these formulations

MATERIALS AND METHODS

Materials

Cefpodoxime proxetil (Orchid Chemical, India) a gift from S. J & G. Fazul Ellahie (Pvt.) Ltd. (Karachi, Pakistan), Fumaric acid (BDH, England), Maleic acid (BDH, England), Citric acid anhydrous (Sigma Aldrich, Germany), Avicel PH 101® (FMC, Brussels, Belgium), Starch 1500® (Colorcon Ltd., England), Magnesium stearate (Fischer, UK). Orelox® tablets as reference brand (Aventis Pvt. Ltd. Karachi, Pakistan) purchased from the local market. All other chemicals, reagents and solvents used were of analytical grade. Software adds in program DD solver®, Microsoft Excel 2013® for statistical analysis and R Gui® 2.13 (CARN Packages) for stability studies were used.

Methods

Manufacturing of tablets

Twelve formulations using three different solid buffers i.e. fumaric acid (F1-F4), maleic acid (M1-M4) and citric acid (C1-C4) were designed for direct compression in such a way that the cefpodoxime (130 mg of cefpodoxime proxetil are equivalent to 100mg of cefpodoxime)(Sharma *et al*., 2011) and each acidifier was taken in the ratios of 4:1, 2:1, 1:1and 1:2 and adjusted by microcrystalline cellulose (Avicel PH 101®) while other excipients such as starch 1500® and magnesium stearate were used in constant concentrations as given in table 1. Materials were blended for 6 minutes in a poly bag using the geometric dilution technique. The blend was compressed using a single-punch tablet machine (Korsch Erweka, Frankfurt, Germany) fitted with a convex shaped punch having a diameter of 13.38 mm to get spherical uncoated tablets weighing 500- 600 mg (±5%). Hardness set for compression ranged between 8-10 kg.

Film coating of tablets

After quality evaluation of uncoated developed formulations, film coating of some selected formulations F3, F4, and M4 was performed to improve the stability of the drug as it is highly susceptible to hydrolyze (Fukutsu *et al*., 2006). The selection of these uncoated formulations for film coating was carried out on the basis of a better drug release profiles in different dissolution media i.e. distilled water, dissolution medium having glycine and sodium chloride in a composition as given in USP (USP, 2013), HCl buffer solution (pH 1.2) and phosphate buffer solutions (pH 4.5 and 6.8) (FDA, 2000) Film coating solution was prepared with the composition as given in Table 2 with following operating conditions (Cole, 1990).

Exhaust air flow rate: 140-160m^{-3} Temperature 20-25°C
Inlet air flow rate: 130-150m^{-3} Temperature: 50-65°C
Relative humidity: 40-60% RH

Quality evaluation of tablets

Physical parameters

Tablets from each batch were tested for physical parameters according to USP guidelines (USP, 2013) and some non-pharmacopoeial methods to evaluate their quality attributes including, weight (Sartorious GmbH; type A 6801), hardness (OSK Fujiwara Hardness Tester, Tokyo, Japan), thickness, diameter variation (vernier caliper CD-6, CSX, Mitutoyo, Japan) and friability tests (H. Jurgens GmbH and Co, Bremen, Germany). Disintegration of tablet from each batch and reference brand was performed in basket rack assembly of disintegration apparatus (Erweka, ZT2, Heusenstamm Germany).

Assay

The assay of reference and test formulations was performed by high performance liquid chromatography (HPLC) method as per USP guidelines (USP, 2013)The suitably filtered (through 0.45µ) and degassed mixture of mobile phase composed of 0.02M Ammonium acetate and acetonitrile (60:40) with a flow rate of 2 ml per minute. A diluent was also prepared by mixing degassed water and acetonitrile in the same ratio. The HPLC was equipped with a 236-nm detector (UV detector SPD 10-AVP, Shimadzu Corp., Tokyo, Japan), a pump LC-10 ADVP, Communication Bus Module (CBM 102) and separation of drug was done by Phenomenex® (250×4.6 mm, 5µm particle size) ODS column with injection volume about 20µl. A standard solution and test sample of each formulation were prepared in diluent in accordance with USP guidelines (USP, 2013). The assay test for each formulation was performed in triplicate.

In vitro dissolution studies

Multiple point dissolution test on tablets from each formulation and reference brand evaluated in different dissolution media according to FDA and USP guidelines (FDA, 2000, USP, 2013) including distilled water, USP dissolution medium, HCl buffer solution of pH 1.2, phosphate buffer solutions of 4.5 and 6.8. Additionally, dissolution study of the selected film coated formulations (F3, F4 and M4), were also performed in biorelevant dissolution media i.e. fasted state of simulated gastric fluid (FaSSGF), fasted state of simulated intestinal fluid (FaSSIF) and fed state of simulated intestinal fluid (FeSSIF), using USP Apparatus II (DT 600, Erweka, Husenstamm, Germany). The dissolution was performed using 900 ml of the dissolution medium and temperature

was maintained at 37±0.5°C with paddle rotating at 75 rpm. An Aliquot of 10 ml from dissolution medium was withdrawn and filtered through Whatman® filter paper no. 41 at different time intervals (5, 10, 15, 20, 25, 30, 45, 60, 90, 120 minutes) and sink condition was maintained by replacing each sample with the same volumes of fresh dissolution medium (10 ml) at each time interval. These samples were suitably diluted with dissolution medium, in comparison with a standard solution having a known concentration of cefpodoxime proxetil, in the same dissolution medium. Drug concentration was calculated by UV-Visible spectrophotometer 1800 (Shimadzu, Kyoto, Japan) at 259 nm with dissolution medium. For each batch samples were analyzed in triplicate.

Comparison of dissolution profiles

A model independent approach was applied on control (CON) and some selected formulations F3, F4 and M4 in comparison with reference formulation (A1) to determine the similarity factor (*f2*) by following equation.

$$f_2=50\times\log\{[1+(1/n)\Sigma_{t=1}^{n}(R_t-T_t)^2]^{-0.5}\times100 \quad (1)$$

Where n is the number of samples, R_t and T_t represent the percentage dissolved of the reference and test product at each time point (Moisei *et al*., 2014).

A model dependent approach was also applied to study the release kinetics of cefpodoxime proxetil test formulations (F3, F4 and M4). Different models including First order, Higuchi, Hixson Crowell and Weibull were applied to analyze dissolution data obtained from distilled water, USP dissolution medium, HCl buffer solution of pH 1.2, phosphate buffer solution of pH 4.5 & 6.8 and bio relevant dissolution media (FaSSGS, FaSSIF and FeSSIF) using the software DD Solver®. The goodness of fit of a model was determined by adjusted coefficient of determination ($r^2_{adjusted}$) and AIC (Akaike Information Criteria) values (Zhang *et al*., 2010). Drug release kinetics through these models can be described by following equations,

First order release

$$\ln Q = \ln Q_o - Kt \quad (2)$$

Where Q is the drug release at time; Q_o is initial drug release at time t and K is the first order rate constant (Banker *et al*., 2002)

Higuchi model

$$Q = K_H\, t^{1/2} \quad (3)$$

Where K_H is the release rate constant, t is the time and Q is the drug release (Higuchi, 1963)

Hixson-crowell cube release model

$$Q_o^{1/3} - Q_t^{1/3} = K_{HC}\, t \quad (4)$$

Where Q_o is the initial amount of drug in the pharmaceutical dosage form. Q_t is the amount of drug release at time t and K_{HC} is constant showing surface to volume relation (Hixson and Crowell, 1931).

Weibull model

$$F(t) = F^{\infty}.(1 - e^{((t+To)/\alpha)\beta)}) \quad (5)$$

Where F (t) is the amount of drug dissolved as a function of time t. F^{∞} is total amount of drug released. T_o is account for lag time measured as a result of the dissolution process. α denotes a scale parameter that describes the time dependence and β is shape parameter (Langenbucher, 1972).

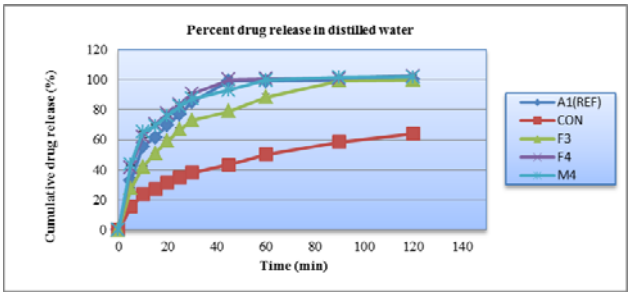

Fig. 1: Release profile of reference, control and film coated test formulations of cefpodoxime proxetil in distilled water

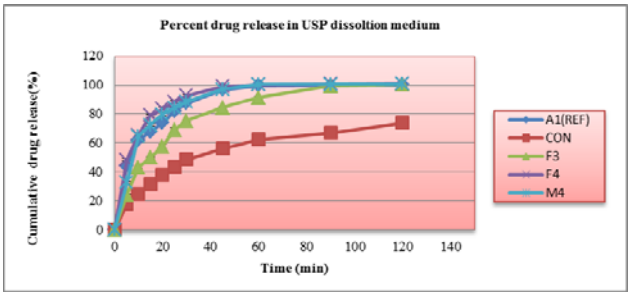

Fig. 2: Release profile of reference, control and film coated test formulations of cefpodoxime proxetil in USP dissolution medium of pH 3

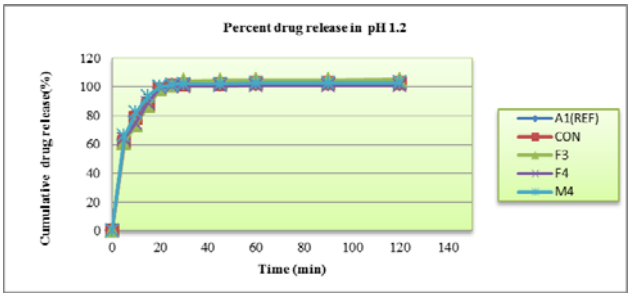

Fig. 3: Release profile of reference, control and film coated test formulations of cefpodoxime proxetil in HCl buffer solution of pH 1.2

Stability studies

Stability test of some selected film coated formulations F3, F4 and M4 was performed under accelerated and long term conditions as per ICH guidelines (ICH, 2003). These formulations were kept in amber glass bottles for six months under accelerated conditions (40±2°C temperature and 75±5% relative humidity) and for one year under long term conditions (25±2°C temperature and 60±5% relative humidity) using a stability chamber (NuAire, USA). Disintegration time, single point dissolution at 30 min and

content uniformity were evaluated at different time intervals according to ICH guidelines. Shelf life of these formulations was estimated by using R Gui Software.

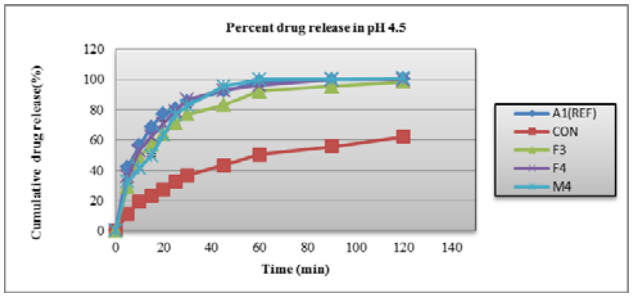

Fig. 4: Release profile of reference, control and film coated test formulations of cefpodoxime proxetil in phosphate buffer of pH 4.5

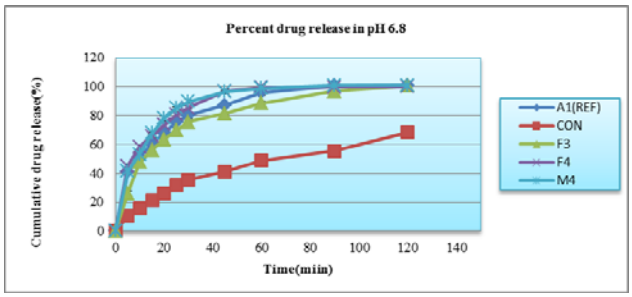

Fig. 5: Release profile of reference, control and film coated test formulations of cefpodoxime proxetil in phosphate buffer of pH 6.8

RESULTS

Cefpodoxime proxetil is an orally administered, extended spectrum, semi-synthetic antibiotic of the cephalosporin class, and has an active metabolite cefpodoxime. It has the widest spectrum of activity among the all tested oral cephalosporins (Merchant *et al*., 2006), but poor water solubility of the drug offers a challenging problem in its formulation designing that ultimately influences its release characteristics and bioavailability (Khan *et al*., 2010). Considering the wide range of activity of cefpodoxime, different trial formulations of cefpodoxime proxetil were prepared by direct compression method using fumaric acid, maleic acid and citric acid, as buffering agents, in different ratios to enhance its solubility. All uncoated formulations i.e. F1- F4 (Fumaric acid formulations), M1-M4 (Maleic acid formulations) and C1-C4 (Citric acid formulations) were evaluated for physicochemical parameters as shown in table 3. Drug release profile of reference and all uncoated test formulations were taken in five different dissolution media including distilled water, USP dissolution medium of pH 3, HCl buffer solution of pH 1.2 and phosphate buffer solutions of pH 4.5 and 6.8. Formulations F3, F4, M4 were selected for film coating on the basis of a better drug release in these media according to USP guidelines (70% drug release within 30 minutes) and also evaluated for physical parameter as shown in table 3. The in vitro dissolution studies of these film coated formulations were also established in biorelevant dissolution media i.e. FaSSGF, FaSSIF and FeSSIF according to FDA guidelines as given in figs. 1-8.

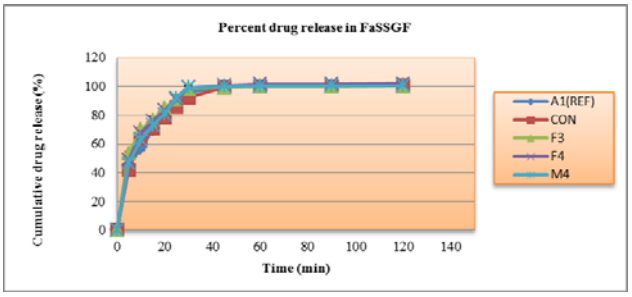

Fig. 6: Release profile of reference, control and film coated test formulations of cefpodoxime proxetil in FaSSGF.

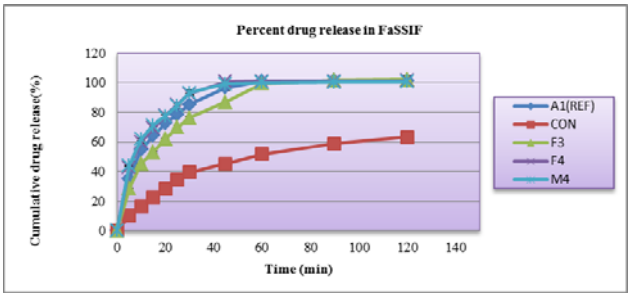

Fig. 7: Release profile of reference, control and film coated test formulations of cefpodoxime proxetil in FaSSIF

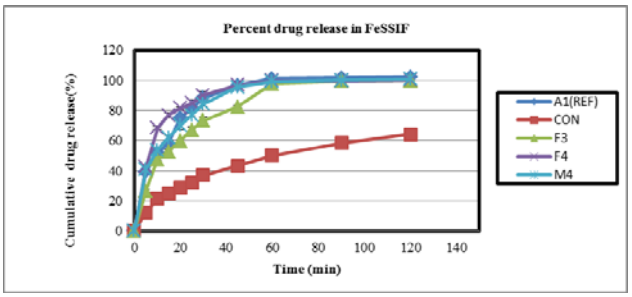

Fig. 8: Release profile of reference, control and film coated test formulations of cefpodoxime proxetil in FeSSIF

The release profile of control (CON) and film coated formulations F3, F4 and M4 was also compared with reference brand A1 through a model independent approach by calculating similarity factor f_2 in different dissolution media (table 4). In vitro release data of reference and test (F3, F4and M4) formulations in various dissolution media were also fitted into different mathematical kinetic models (table 5). The drug release was found best fitted to the Weibull model on the basis of best goodness of fit ($r^2_{adjusted}$) and AIC values. Accelerated and long term stability studies of film coated formulations F3, F4 and M4 were performed according to ICH guidelines and shelf life was determined by using R Gui® 2.13 software (table 6, figs. 9-10).

Table 1: Composition of cefpodxime proxetil formulations

Ingredients	Formulations*												
	CON	F1	F2	F3	F4	M1	M2	M3	M4	C1	C2	C3	C4
	mg	mg	mg	mg	mg	mg	mg	mg	mg	mg	mg	Mg	mg
Cefpodoxime proxetil	130	130	130	130	130	130	130	130	130	130	130	130	130
Fumaric acid	-	25	50	100	200	-	-	-	-	-	-	-	-
Maleic acid	-	-	-	-	-	25	50	100	200	-	-	-	-
Citric acid	-	-	-	-	-	-	-	-	-	25	50	100	200
Avicel PH 101	315	290	265	265	215	290	265	265	215	290	265	265	215
Starch 1500	50	50	50	50	50	50	50	50	50	50	50	50	50
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5	5
Total compression weight per tablet	500	500	500	550	600	500	500	550	600	500	500	550	600

*Formulation code CON= Control formulation (cefpodoxime proxetil only) ,F1= cefpodoxime and fumaric acid (4:1),F2 = cefpodoxime and fumaric acid (2:1), F3 = cefpodoxime and fumaric acid (1:1), F4= cefpodoxime and fumaric acid (1:2) , M1= cefpodoxime and maleic acid(4:1), M2 = cefpodoxime and maleic acid (2:1), M3 = cefpodoxime and:maleic acid (1:1) , M4 = cefpodoxime and maleic acid (1:2), C1= cefpodoxime and citric acid (4:1), C2 = cefpodoxime and citric acid (2:1), C3 = cefpodoxime and citric acid in (1:1), C4= cefpodoxime and citric acid (1:2). *Each formulations contains 130 mg of cefpodoxime proxetil per tablet equivalent to 100mg of cefpodoxime

Table 2: Composition of film coating solution

Ingredients	Quantity
HPMC (15 cps)	300g
propylene glycol	50g
Lake (D & C red 27, 21, NDFC yellow 2190)	Qs.
Methylene chloride	6.0L
Industrial methylated spirits (ethanol)	4.5L

Table 3: Physicochemical properties of reference and test formulations of cefpodoxime proxetil tablets

Code	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Hardness (kg)	Friability (%)	Disintegration (sec)	Assay (%)
A1 (REF)	230.02±1.64	4.34±0.03	9.26±0.03	N/A	N/A	58.33±0.58	100.18±0.29
Uncoated formulations							
Control	502.97±3.30	3.40±0.09	13.36±0.08	8.45±0.15	0.75±0.08	55.67±1.15	100.41±0.83
C1	501.53± 1.50	3.43±0.08	13.36±0.08	8.68±0.15	0.48±0.09	56.00±1.73	100.60±1.01
C2	501.66±2.65	3.40±0.09	13.38±0.07	8.58±0.21	0.40±0.06	62.33±0.58	99.87±0.50
C3	551.18±1.39	4.32±0.04	13.39±0.07	8.33±0.08	0.60±0.08	59.33±1.53	100.85±0.62
C4	603.03±3.39	4.41±0.06	13.41±0.07	8.34±0.09	0.73±0.11	57.00±1.73	100.31±0.29
M1	502.43±1.55	3.36±0.10	13.37±0.05	9.49±0.17	0.47±0.10	61.00±1.00	96.03±0.27
M2	502.12±2.36	3.44±0.09	13.40±0.07	9.45±0.16	0.38±0.11	58.67±1.53	101.45±0.44
M3	551.05±1.09	4.30±0.04	13.39±0.05	8.35±0.13	0.69±0.08	57.67±0.58	100.33±0.60
M4	602.60±2.06	4.40±0.05	13.38±0.07	8.41±0.15	0.68±0.06	62.00±2.00	99.71±1.35
F1	501.37±1.25	3.37±0.07	13.41±0.04	9.56±0.20	0.40±0.11	64.33±1.15	100.63±1.07
F2	501.62±1.54	3.38±0.10	13.38±0.05	9.37±0.16	0.37±0.09	64.67±2.52	99.09±3.58
F3	550.92±1.34	4.32±0.04	13.39±0.05	8.42±0.21	0.63±0.12	62.33±0.58	100.37±1.13
F4	601.01±2.06	4.40±0.06	13.35±0.08	8.47±0.27	0.69±0.12	64.33±1.15	101.08±1.67
Film coated formulations							
F3	581.24±2.87	5.20±0.05	14.44±0.07	N/A	N/A	69.33±1.63	101.80±0.36
F4	630.48±1.44	5.46±0.03	14.46±0.07	N/A	N/A	72.00±1.79	101.17±0.34
M4	629.55±1.20	5.45±0.04	14.61±0.04	N/A	N/A	71.67±1.03	100.74±0.95

Table 4: Similarity factor (*f2*) values of control and film coated test formulations Cefpodoxime proxetil with Reference (A1) in different dissolution media

S. No	Code	Factor	D.W*	D.M*	HCl buffer pH 1.2	Phosphate buffer pH 4.5	Phosphate buffer pH 4.5	FaSSGF*	FaSSIF*	FeSSIF*
1	CON	*f2*	19.68	22.63	N/A*	17.68	19.41	77.58	18.53	18.22
2	F3	*f2*	48.00	43.19	N/A	52.48	59.26	61.79	55.02	48.91
3	F4	*f2*	61.54	60.52	N/A	57.18	62.95	66.58	64.84	53.69
4	M4	*f2*	60.00	64.51	N/A	51.15	58.31	75.68	62.35	74.75

*****D.W (Distilled water), *D.M (USP dissolution medium of pH 3), *FaSSGF (Fasted state of simulated gastric fluid), *FaSSIF (Fasted state of simulated intestinal fluid), *FeSSIF (Fed state of simulated intestine al fluid), *N/A (not applicable since drug release was found more than 80% within 15min)

Table 5: *In vitro* release kinetics of reference and selected test formulations

Code	First order			Higuchi			Hixson-Crowell			Weibull		
	$r^2_{adjusted}$	K_1	AIC	$r^2_{adjusted}$	K_H	AIC	$r^2_{adjusted}$	K_{HC}	AIC	$r^2_{adjusted}$	β	AIC
Distilled water												
REF	0.975	0.067	49.841	0.361	12.192	82.235	0.701	0.013	74.633	0.982	0.878	48.361
CON	0.612	0.013	69.170	0.957	6.381	47.266	0.443	0.004	72.803	0.998	0.551	18.416
F3	0.965	0.045	54.150	0.804	11.053	71.294	0.894	0.012	65.148	0.992	0.789	41.021
F4	0.964	0.086	50.722	-0.179	12.723	85.735	0.257	0.013	81.118	0.985	0.813	43.793
M4	0.904	0.084	59.154	-0.279	12.535	84.998	0.114	0.013	81.321	0.983	0.688	44.055
Dissolution medium												
REF	0.926	0.081	57.000	-0.244	12.480	12.480	0.205	0.013	80.693	0.983	0.723	44.127
CON	0.748	0.018	68.622	0.918	7.625	7.625	0.566	0.005	74.059	0.989	0.602	39.150
F3	0.987	0.047	45.565	0.797	11.228	11.228	0.936	0.012	61.149	0.994	0.877	39.795
F4	0.967	0.107	47.003	-1.174	12.990	12.990	-0.582	0.014	85.704	0.996	0.785	27.649
M4	0.978	0.087	47.108	-0.121	12.663	12.663	0.306	0.013	81.601	0.981	0.921	47.776
pH 1.2												
REF	0.948	0.177	46.044	-5.364	13.794	94.120	-4.508	0.014	92.676	0.958	0.867	45.821
CON	0.947	0.168	47.483	-4.324	13.800	93.609	-3.574	0.014	92.091	0.955	0.880	47.796
F3	0.926	0.171	49.675	-5.221	13.671	93.963	-4.297	0.014	92.355	0.944	0.833	48.895
F4	0.934	0.191	48.462	-5.773	14.002	94.799	-5.016	0.014	93.614	0.935	0.958	50.328
M4	0.948	0.199	44.603	-6.970	13.969	94.850	-6.140	0.014	93.751	0.952	0.904	45.654
pH 4.5												
REF	0.949	0.077	53.804	-0.074	12.333	84.226	0.342	0.013	79.331	0.995	0.739	31.924
CON	0.770	0.012	65.411	0.975	6.081	43.100	0.650	0.003	69.598	0.992	0.619	33.239
F3	0.950	0.054	55.942	0.569	11.350	77.422	0.786	0.012	70.416	0.995	0.738	34.579
F4	0.962	0.060	54.496	0.499	11.926	80.248	0.788	0.013	71.647	0.969	0.872	54.292
M4	0.974	0.055	52.712	0.657	11.873	78.511	0.900	0.013	66.192	0.974	1.004	54.710
pH 6.8												
REF	0.920	0.062	59.530	0.397	11.888	79.698	0.647	0.013	74.342	0.985	0.707	45.082
CON	0.895	0.012	59.630	0.984	6.092	40.692	0.825	0.003	64.737	0.991	0.711	36.758
F3	0.954	0.050	55.900	0.688	11.254	75.126	0.840	0.012	68.443	0.991	0.760	41.460
F4	0.918	0.077	58.274	-0.100	12.383	84.292	0.318	0.013	79.505	0.979	0.717	46.585
M4	0.977	0.080	46.990	-0.008	12.547	84.909	0.415	0.013	79.477	0.989	0.850	41.817
FaSSGF												
REF	0.895	0.086	51.316	-0.208	12.864	86.931	0.202	0.014	82.252	0.924	0.786	49.751
CON	0.989	0.089	48.807	-0.351	12.735	86.633	0.135	0.013	82.182	0.988	0.822	41.291
F3	0.928	0.116	53.262	-1.842	13.093	90.058	-1.142	0.014	87.232	0.990	0.741	43.306
F4	0.958	0.108	50.326	-1.025	13.173	89.149	-0.475	0.014	85.981	0.975	0.834	47.298
M4	0.960	0.099	50.763	-0.741	12.986	88.619	-0.475	0.014	85.981	0.970	0.868	49.951
FaSSIF												
REF	0.962	0.088	47.707	-0.335	12.864	82.344	0.164	0.013	75.695	0.962	0.850	42.804
CON	0.820	0.012	64.564	0.960	6.275	49.494	0.710	0.003	69.319	0.981	0.655	43.865
F3	0.980	0.052	49.797	0.753	11.651	74.716	0.918	0.012	63.730	0.985	0.890	48.471
F4	0.968	0.086	49.744	-0.193	12.751	86.086	0.259	0.013	81.326	0.989	0.841	45.586
M4	0.959	0.089	51.417	-0.392	12.728	86.609	0.100	0.013	82.242	0.985	0.797	43.430
FeSSIF												
REF	0.966	0.071	52.856	0.325	12.429	82.634	0.655	0.013	75.921	0.973	0.880	52.576
CON	0.769	0.012	65.522	0.984	6.251	38.737	0.647	0.003	69.765	0.998	0.615	21.928
F3	0.965	0.049	54.678	0.758	11.357	73.913	0.897	0.012	65.352	0.981	0.829	50.557
F4	0.955	0.098	51.035	-0.792	12.760	87.835	-0.251	0.014	84.238	0.987	0.773	40.424
M4	0.944	0.068	56.256	0.273	12.203	81.960	0.606	0.013	75.826	0.979	0.770	48.654

DISCUSSION

The solubility of drug is one of the challenging aspect in formulation development (Senthilkumar *et al*., 2012). It has been observed that poorly water soluble drugs are given usually in high doses to obtain the desired pharmacological effects after oral administration, but this approach is not appropriate to develop an oral dosage formulation, since it may contribute risk to the patient as well as cost of the product will be enhanced (Israr *et al*., 2014). Research should be done to improve the solubility of the compound, so that maximum desirable therapeutic outcome can be obtained in suitably minimal doses.

In present study cefpodoxime proxetil, BCS class IV drug was chosen as model drug and its different formulations

Table 6: Stability studies of selected film coated cefpodoxime proxetil formulations at 25°C and 40°C (ambient and accelerated temperatures)

Long term stability studies (25 ± 2 ^{0}C / 60 ± 5%RH)					
Code	Study period (months)	Disintegration (seconds)	Drug content (%)	Dissolution (%) (at 30 min)	Shelf life
F3	0	63	101.92	76.16	33
	3	58	101.03	74.93	
	6	61	100.65	75.43	
	9	65	99.31	77.12	
	12	67	98.22	76.65	
F4	0	71	102.45	92.65	33
	3	73	101.98	90.95	
	6	69	100.65	93.23	
	9	71	99.45	90.89	
	12	67	98.88	92.65	
M4	0	58	100.45	88.89	0
	3	60	79.65	68.04	
	6	61	57.35	46.12	
	9	57	40.45	32.45	
	12	55	20.31	14.34	
Stability studies under accelerated conditions (40 ± 2^{0}C / 75 ± 5% RH)					
F3	0	66	102.89	77.61	28
	1	69	102.15	75.16	
	3	63	101.65	76.89	
	6	72	100.35	75.88	
F4	0	61	101.77	91.89	27
	1	67	101.02	92.13	
	3	70	100.75	92.45	
	6	59	99.88	91.78	
M4	0	55	100.89	89.54	0
	1	63	50.35	33.45	
	3	60	20.45	11.36	
	6	59	5.15	4.34	

were developed by incorporation of solid buffers (fumaric acid, maleic acid and citric acid), which is one of applied strategies by many researchers to improve the solubility of poorly water soluble drugs (Ahjel and Lupuleasa, 2009, Riis *et al*., 2007, Kranz *et al*., 2005) Twelve different formulations using fumaric acid, maleic acid and citric acid as buffering agents were prepared by direct compression method, in drug to fumaric acid ratios of F1(4:1), F2 (2:1), F3(1:1), F4 (1:2) , drug to maleic acid ratios of M1 (4:1), M2 (2:1), M3 (1:1), M4 (1:2), and drug to citric acid ratio of C1 (4:1), C2 (2:1), C3(1:1) and C4 (1:2). A control formulation (CON) without incorporation of any of these buffers was also prepared for comparative evaluation (table 1). Direct compression method was adopted for its convenience, cost effectiveness and reason to give a stable product (Shangraw, 1998) and it is a widely used reported method by many formulation scientists in preparing oral dosage forms. (Muhammad *et al*., 2012, Chintan *et al*., 2012, Martinello *et al*., 2006). After compression, quality evaluation of all uncoated formulations was performed through different tests including weight, thickness, diameter, hardness variation and friability tests in accordance with USP guidelines(Badalkumar *et al*., 2012, Kukati *et al*., 2014, Vinay *et al*., 2014). On the basis of quality evaluation and in vitro drug release studies the formulations F3, F4 and M4 were selected for film coating and further subjected to quality evaluation after coating. All formulations were found within the specified limits of weight variation i.e. 501.53±1.50 to 603.03±3.39 mg of uncoated formulations and from 581±2.87 to 630.48±1.44 mg of film coated formulations (table 3). The thickness and diameter variation of all formulations were also within the limits of ±5% SD (table 3) according to USP (USP, 2013) . For a satisfactory tablet, hardness of more than 4kg is usually considered suitable and is used as a guide in compression (Allen and Ansel, 2013). For hardness of all uncoated formulations, the results were found in the range of 8.33kg±0.08 to 9.56±0.20kg and friability was observed less than 1% (table 3).

Fig. 9: Physical appearance of selected film coated cefpodoxime proxetil formulations during long term stability studies at 25°C

The immediate release tablets must be disintegrated from its intact form and get dissolved to show suitable release kinetics. Thus the addition of the right disintegrant is very important for best possible bioavailability (Bhowmik *et al*., 2010). Starch 1500® (pregelatinized starch) is widely used as a disintegrant in tablet manufacturing to improve the disintegration and dissolution performance (Rahman *et al*., 2008). In present study, the disintegration time of all formulations using starch 1500® as disintegrant was found within the specified limits of USP i.e. 55.67±1.15 to 64.67±2.52 seconds for uncoated formulations and from 55.67±1.15 to 72.00±1.79 seconds for coated formulations (table 3). A high performance liquid chromatography technique (HPLC) was used to perform pharmaceutical assay of all formulations. Assay results of all formulations (table 3) were found within limits i.e. 90-110% as shown in table 3 (USP, 2013).

In vitro dissolution testing provides guidance on optimizing drug release from pharmaceutical formulations. It is also applied as an indicator of the in vivo performance of drug products (Ahuja *et al*., 2005). Previously in many research works, for optimization of a formulation, dissolution profile of trial formulations has been analyzed and compared in distilled water, official dissolution medium (USP), HCl buffer solution of pH 1.2 and phosphate buffer solutions of pH 4.5 and 6.8 (Ahmad *et al*., 2015, Zafar *et al*., 2012). Similarly, in vitro drug release data of all developed and reference formulations (A1) was also determined and compared. In 0.1N HCl solution of pH 1.2, all formulations showed a drug release up to 100% within 15-20min as cefpodoxime proxetil is weakly basic drug and highly soluble at pH 1.2 (V Kamalakkannan *et al*., 2013). So results were not comparable for optimization of formulations at pH 1.2,

Fig. 10: Physical appearance of selected film coated cefpodoxime proxetil formulations during accelerated stability studies at 40°C

but a marked difference was observed among all test formulations when drug release data was determined in all above mentioned media except at pH 1.2 and served as base line to optimize formulations.

The dissolution data of formulation F1 and F2 with fumaric acid showed a poor release of drug (34.00± 0.79 to 54.44±1.35%) within 30 min of observation in different media used. When proportion of fumaric acid was increased in equal ratio with cefpodoxime, formulation F3 showed a marked increase in dissolution of the drug (73.12±2.35 to 76.43±0.88%) within 30 min. Whereas drug release profile of formulation F4 having twice proportion of fumaric acid, showed a high increase in dissolution in the given media, (85.97±2.25 to 95.64± 0.85) within 30 min. The study revealed that fumaric acid has shown a promising effect on dissolution enhancement of cefpodoxime proxetil.

Similarly the in vitro cefpodoxime proxetil release from formulations M1 and M2 was found poor i.e. 35.27±0.79 to 55.63±0.66% within 30 min in dissolution media. But after increasing the proportions of maleic acid in formulation M3 and M4, a better release profiles were observed i.e. 51.01±0.69 to 76.91±0.93% and 83.22±1.77 to 90.34±0.88% respectively. A very low drug release (36.49±0.66 to 59.73±0.84% within 30 min) was found from dissolution profiles of formulations C1, C2, C3 and

C4 showing no effect of citric acid on the dissolution enhancement of cefpodoxime proxetil.

The dissolution profiles of film coated Formulations F3, F4 and M4 were also performed in the same dissolution media and similar release profiles were obtained as given by uncoated tablets. For film coated formulations percentage drug release was also determined in biorelevant dissolution media and drug content was found in the range of 98 to 99% in FaSSGF for all selected formulations. Fumaric acid exhibited substantial improvement on dissolution profile of F3 formulation having drug in equal ratio i.e. 59.91±0.79 to 76.27±0.73% (within 30 min) in FeSSIF and FaSSIF respectively. Whereas fumaric acid and maleic acid showed a remarkable effect on in vitro release of the drug (82.54±0.65 to 92.67±0.71%) in these media when used in twice proportion (Formulations F4& M4) as shown in Fig. 1 to 8.

On the basis of maximum drug release F4 and M4 were selected as the best formulations among all trial batches. Incorporation of these acidifiers in an appropriate proportions maintained the acidic micro environment around the tablets of weakly basic drugs to make the drug release pH independent throughout GIT (Streubel *et al*., 2000). Similar results were also observed when effect of fumaric, citric and itionic acids on verapamil-hydrochloride tablets (weakly basic drug) was observed (Dvorackova *et al*., 2013).

Both model independent and model dependent approaches have been widely applied to analyze and compare dissolution data of various drugs by many researchers in recent years (Husain *et al*., 2016, Israr *et al*., 2015). When control and film coated formulations (CON, F3, F4 and M4) were compared with reference formulation (A1), the similarity factor (*f*2) for control (CON) was found less than 50 (table 4). Formulation F3 exhibited similarity in drug release profile with the reference formulation at phosphate buffer (pH 4.5 and 6.8), FaSSGF and FaSSIF with *f2* values i.e. 52.48, 59.26, 61.79 and 55.02 respectively. The similarity factor for formulations F4 and M4 was also found greater than 50 in all media (table 4). Model independent approach was not applied for the release profiles obtained at pH 1.2, since more than 85% of drug release occurred within 15 minutes (FDA, 2000).

A model dependent approach through different kinetic models using DD solver® software has been widely used by many researchers for the optimization of formulation (Husain *et al*., 2016, Zhang *et al*., 2010, Zuo *et al*., 2014, Dash *et al*., 2010) In present work this approach was applied through various kinetic models i.e. First order, Higuchi, Hixson Crowell and Weibull to evaluate drug release kinetics of reference (A1), control (CON) and test formulations (F3, F4 and M4) in all media used (table 5). The drug release was found to best fit the Weibull model as highest value of r^2_{adjusted} were obtained i.e. 0.924 to 0.973 for reference formulation (A1), 0.955 to 0.998 for control formulation (CON), and 0.944 to 0.994 for test formulation (F3), 0.935 to 0.996 for F4 and 0.952 to 0.989 for M4. Furthermore lowest AIC values were also found through this model i.e. 31.924 to 52.576 (A1), 18.461 to 43 (CON), 34.579 to 50.557 (F3), 27.469 to 40.424 (F4) and 43.430 to 44.055 (M4) (table 5). The values of shape parameter β for reference and all test formulations were found less than 1 indicating that all formulations showed parabolic curve with a steeper initial slope. The drug release was first order with r^2_{adjusted} values closer to 1, but could not be chosen as best fit model due to higher AIC values in comparison with Weibull model (table 5). In present study formulations F4 and M4 were found close in terms of their drug release kinetics. Previously similar approach was also applied to analyze the dissolution data of cefpodoxime proxetil extended release tablets followed Korsmeyer-Peppas model (Merchant *et al*., 2006). In an another work dissolution profiles of floating tablets of cefpodoxime proxetil were compared and analyzed through different kinetics models and it was found that the release of the drug from these formulations followed zero order kinetics and mechanism of release was anomalous (Kukati *et al*., 2014).

Stability studies

The chemical and physical stability of a drug substance alone and when combined with formulation ingredients, is a critical issue in designing a successful pharmaceutical product (Allen and Ansel, 2013). Many researchers have performed accelerated and long term stability studies of tablet formulations in accordance with ICH guidelines (Oliveira *et al*., 2013, Sekar and Chellan, 2008) In present study accelerated and long term stability studies of selected film coated formulation F3, F4 and M4 were also performed in the same way for 6 and 12 months respectively. Disintegration time, single point dissolution (at 30 min) and content uniformity was determined at different time interval. Shelf life of these formulations was also estimated under both conditions by using R Gui® 2.13 software (table 6). Formulation F3 and F4 was found to be stable with a shelf life of 28 and 27 months under accelerated conditions and 33 months when kept for long term for one year with no change in color and appearance (fig. 9 &10). While formulation M4 showed a marked physical and chemical drug interaction of cefpodoxime proxetil with maleic acid and was found to be unstable with decrement in dissolution and assay results showed major changes in its color and texture (figs. 9-10).

CONCLUSION

Twelve trial formulations of cefpodoxime proxetil were prepared successfully by direct compression technique to

observe the effects of organic acids (Fumaric, maleic and citric acid) in different concentrations to enhance the dissolution of the drug. On the basis of drug release three formulations (F3, F4 and M4) were selected for film coating to protect the drug from any chemical degradation. Formulation F4 and M4 showed promising results with highest dissolution rate which were further optimized through model independent and dependent approaches. When these formulations were kept for stability studies formulation F3 and F4 were found to be stable, while formulation M4 exhibited clear signs of physical and chemical degradation. Therefore, formulation F4 was chosen as best formulation on the basis of physical properties, highest dissolution rate and stability.

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